PINS AND NEEDLES – INJURY AND REGENERATION IN THE PERIPHERAL NERVOUS SYSTEM

What is the Peripheral Nervous System?

- the peripheral nervous system (PNS) comprises **all components of the nervous system that lie outside the brain and spinal cord** (the central nervous system or CNS)
- the PNS can be broadly divided into **sensorimotor**, **autonomic** and **enteric divisions** and includes:

  - **dorsal (sensory)** and **ventral (motor) spinal roots**
  - **spinal ganglia - dorsal root ganglia** which contain primary sensory neurons
  - **spinal nerves**
  - **peripheral nerves**
  - **cranial nerves** and their **sensory ganglia**
  - **enteric nerves** and their **ganglia** in the submucosal and myenteric plexuses of the alimentary tract
  - **sympathetic** and **parasympathetic autonomic ganglia** and their **pre-ganglionic and post-ganglionic nerve fibres**

- **Schwann cells** are responsible for myelination and maintenance of axons in the PNS
- they also secrete neurotrophic factors that play a role in regeneration of peripheral nerves

Clinical Signs of Peripheral Neuropathies

- many diseases of the CNS also involve the PNS, either because of damage to the nerve cell bodies in the CNS or because the CNS and PNS are equally vulnerable to the disease process
- some disorders primarily affect only the PNS

- PNS disease may manifest as a **mononeuropathy** (i.e. involving a single nerve) or a **polyneuropathy** (involving multiple nerves)

- **clinical signs of PNS disease** include denervation atrophy of skeletal muscles, paresis (weakness) or flaccid paralysis of innervated structures, diminished or absent reflexes and diminished muscle tone, diminished pain responses, proprioceptive deficits and paraesthesia (abnormal or inappropriate sensation) (e.g. pins and needles)

Denervation Atrophy of Skeletal Muscle

- **denervation atrophy** (= **neurogenic atrophy**) **of skeletal muscle** is **common in domestic animals**, especially following traumatic injury to peripheral nerves
- e.g. laryngeal hemiplegia in horses due to injury to the left recurrent laryngeal nerve
- e.g. injury to the suprascapular nerve in work horses from ill-fitting collars
- e.g. radial nerve paralysis in dogs and cats following car accidents

- it can also follow injury to neuromuscular junctions or spinal roots, or to the nerve cell bodies of motor neurons in the ventral horns of spinal grey matter, the brainstem or the cerebral motor cortex
- e.g. traumatic brachial plexus avulsion in dogs or cats (see below)
- e.g. spinal cord or nerve root damage from vertebral osteomyelitis, trauma, neoplasia or

intervertebral disc protrusion etc. (Lecture 23)
- e.g. myasthenia gravis (see below)

- the myofibre atrophy is due to loss of motor stimuli and normal low-level tonic stimuli
- denervated type 1 (aerobic, slow contraction, slow fatigue) muscle fibres tend to atrophy more rapidly than denervated type 2 (anaerobic, fast contraction) muscle fibres because the former depend on a low level of continuous trophic stimulation from motor axons

- denervation atrophy is always associated with **muscle paralysis** but the latter may be subtle if the affected nerve is small
- denervation atrophy is characterised by **rapid reduction in muscle volume** (e.g. two-thirds of muscle mass may be lost within 2-3 weeks of cessation of motor stimuli)

- denervation atrophy of muscle can be reversible (if the underlying cause of denervation is reversible)
- successful reinnervation of the affected myofibres may allow complete restoration of muscle mass over time (via myofibre hypertrophy) and a return to full muscle function
- however, very advanced lesions (e.g. after a year or more of denervation) may be irreversible as many of the affected fibres may contain no myofibrils or myofilaments and there may have been fibrofatty connective tissue replacement of the lost muscle mass

DEGENERATION AND REGENERATION OF PERIPHERAL NERVES

Wallerian Degeneration

- **Wallerian degeneration** is the term used to describe the degenerative events that follow either acute focal injury to a myelinated axon (Figure 1) or death of its neuronal cell body
- if the neuronal cell body dies, the entire axon will undergo Wallerian degeneration
- if there is focal injury to a myelinated axon, the segment distal to (and just proximal) to the site of injury will undergo Wallerian degeneration

- the events of Wallerian degeneration occur rapidly in the PNS
- within 24 hours of injury, disruption of axoplasmic flow in the damaged axon → swelling of the distal segment of the axon to form an **axonal spheroid**
- within 48 hours of injury, influx of calcium ions into the damaged axon → proteolytic destruction of neurofilaments → collapse, fragmentation and disintegration of the axon

- axonal disintegration renders the myelin sheaths redundant
- from 1-4 days post-injury, the myelin retracts and fragments to form droplets (termed **ellipsoids**) which surround the axonal debris
- this is a form of **secondary demyelination**
- the axonal and myelinic debris is then removed by phagocytosis by macrophages which become filled with lipid vacuoles (they are then referred to as **gitter cells**)
- Schwann cells may also assist in phagocytosis of the debris
- myelin degeneration is usually complete by the end of week 2 although some myelin debris may still persist for several months post-axonal injury

Figure 1

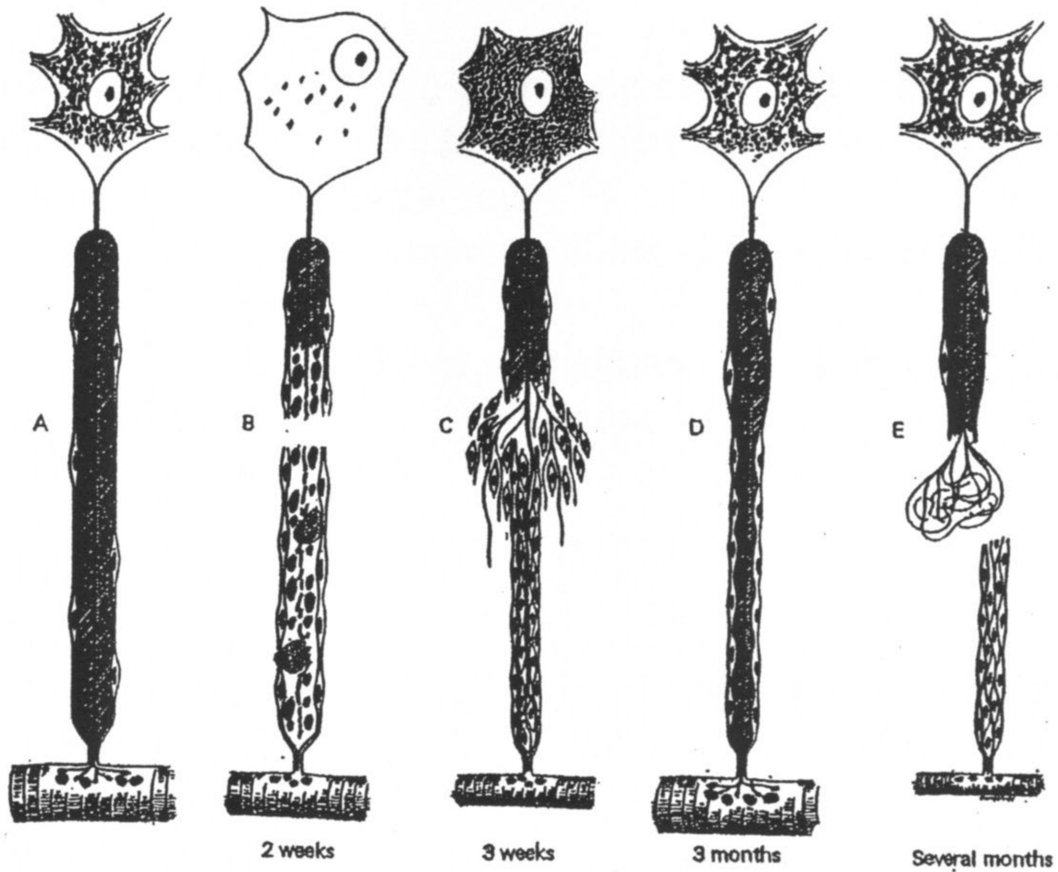

Figure 8–24. Main changes that take place in an injured nerve fiber. *A:* Normal nerve fiber, with its perikaryon and the effector cell (striated skeletal muscle). Note the position of the neuron nucleus and the amount and distribution of Nissl bodies. *B:* When the fiber is injured, the neuronal nucleus moves to the cell periphery and Nissl bodies become greatly reduced in number. The nerve fiber distal to the injury degenerates along with its myelin sheath. Debris is phagocytosed by macrophages. *C:* The muscle fiber shows a pronounced disuse atrophy. Schwann cells proliferate, forming a compact cord penetrated by the growing axon. The axon grows at a rate of 0.5–3 mm/d. *D:* In this example, the nerve fiber regeneration was successful. Note that the muscle fiber was also regenerated after receiving nerve stimuli. *E:* When the axon does not penetrate the cord of Schwann cells, its growth is not organized. (Redrawn and reproduced, with permission, from Willis RA, Willis AT: *The Principles of Pathology and Bacteriology,* 3rd ed. Butterworth, 1972.)

Reference: Junqueira LC, Carneiro J. *Basic Histology*. 3rd edition. Lange Medical Publications, Los Altos, California (1980), p. 178.

Peripheral Nerve Regeneration

- provided that the nerve cell body survives, regeneration of the axon can occur from the proximal stump
- the rate of regeneration is slow and apparently limited by the rate of slow axonal transport to approximately 1-4 mm/day; the rate tends to be slower the greater the distance between the growing tip and the cell body

- the **degree of regeneration depends on the integrity of the endoneurial tube distal to the site of axonal injury**
- the endoneurial tube is composed of the outermost **endoneurium** (connective tissue) and (internal to this) the **basal lamina of the Schwann cells**

- as the axonal and myelinic debris is cleared away, Schwann cells begin to proliferate (C in Figure 1) and form a longitudinal column (**Bungner's bands**) along the former course of the axon
- **if the endoneurial tube remains intact** (e.g. following nerve compression), regenerating sprouts from the proximal axonal stump can enter the tube and ultimately re-establish connection to the end organ (e.g. a skeletal muscle)
- subsequently, the regenerated axon will be remyelinated by Schwann cells

- **if the endoneurial tube is no longer intact** (e.g. if a peripheral nerve is severed), the Schwann cell bands persist and usually endoneurial fibrosis develops → a tangled mass of collagen, Schwann cells and axonal sprouts → failure of reinnervation (E in Figure 1)

Amputation Neuroma

- amputation neuromas are good examples of abortive regeneration following focal axonal injury
- an amputation neuroma may result from traumatic transection of peripheral nerves if a large gap exists between the proximal and distal nerve stumps (or the distal stump has been amputated) → abortive regenerative attempts from the proximal stump → formation of a firm, bulbous, tumour-like mass of tangled axonal sprouts, collagen (scar tissue) and Schwann cells
- amputation neuromas are painful and may provoke self-mutilation

- e.g. post-tail docking in dogs (especially cocker spaniels)
- e.g. following digital nerve resection in horses to treat navicular disease
- e.g. excessive debeaking in chickens

- the processes of Wallerian degeneration and subsequent axonal regeneration differ somewhat in the PNS and the CNS (see Lecture 23)
- in short, Wallerian degeneration proceeds more rapidly in the PNS than in the CNS and the **probability of subsequent regeneration and remyelination of damaged axons is much greater in the PNS than in the CNS**

PERIPHERAL NERVE TRAUMA

- **peripheral neuropathies in domestic animals are most often due to physical trauma**
- traumatic injuries include compression, contusion (bruising), stretching, tearing, laceration and transection

- **iatrogenic injury** to peripheral nerves may result from surgical trauma, application of tight casts or splints, injections (e.g. from direct needle trauma to nerves, injection of irritants, secondary nerve compression by injection-induced haemorrhage or fibrosis) etc.

- mild trauma to peripheral nerves (e.g. mild compression) may cause a temporary local block in conduction of action potentials (without necessarily causing axonal degeneration) → return of function in days to weeks
- more severe trauma (including prolonged or severe compression) → classical Wallerian degeneration at and immediately distal to the level of injury, with variable prospects of future successful regeneration

Avulsion of the Brachial Plexus

- seen most often in cats and dogs due to severe forelimb abduction or traction during car accidents
- usually involves either all roots of the brachial plexus (C_6-T_1) or only the C_8 and T_1 roots
- usually due to tearing of the intradural spinal nerve roots, especially the ventral motor roots
- may present as radial nerve paralysis
- total avulsion of the plexus → permanent flaccid paralysis of the affected forelimb, with denervation atrophy of forelimb muscles and sensory loss distal to the elbow

Post-parturient Paralysis in Cattle

- common in heifers with dystocia due to an oversized fetus
- characterised by recumbency, hindlimb abduction and inability to rise
- thought to result from bilateral compressive damage to the **obturator nerves** as they course over the medial aspects of the iliac shafts + simultaneous bilateral compressive injury to the lumbar (L_6) roots of the **sciatic nerves** as they course over the ventral aspect of the sacrum
- initial nerve trauma may be compounded by prolonged recumbency, especially if more weight is placed on one hindlimb than the other
- e.g. gravitational pooling of blood +/- external venous compression by the cow's weight → venous thrombosis → ischaemic necrosis (especially of the semitendinosus muscle)
- e.g. further compressive damage to the sciatic and peroneal nerves due to the weight of the animal
- similar complications may develop in other "downer cows" (e.g. those with milk fever) if recumbency exceeds 12 hours' duration and a hindlimb is drawn up under the body

Congenital Femoral Nerve Paralysis in Large Calves

- unilateral (especially right) femoral nerve paralysis is common in large Charolais, Simmental, Maine Anjou and Holstein calves following their assisted delivery from dystocic heifers
- a large calf in cranial presentation may fail to enter the vagina if one or both stifle joints engage(s) the pelvic brim
- subsequent traction on the calf's forelimbs → stretching of the quadriceps muscle, its blood vessels and the femoral nerve → contusion or partial or complete tearing of the femoral nerve and quadriceps muscle

Cauda Equina Syndome in Dogs

- occurs in dogs as a result of chronic traumatic damage to the spinal roots of the **cauda equina** (i.e. roots arising from spinal segments L_7, S_1-S_3 and Cocc.$_1$-Cocc.$_5$)
- usually due to **lumbosacral stenosis** and/or **stenosis of the intervertebral foramina**
- **small dog breeds** - usually due to congenital lumbosacral stenosis
- **large dog breeds** (especially male German shepherds) - cumulative degenerative changes are usually responsible for stenosis (e.g. vertebral instability arising from discospondylitis, disc herniation etc.) (Lecture 23)
- clinical signs are usually insidious in onset and may include paresis and atrophy of hindlimb muscles, faecal and urinary incontinence, tail and anal sphincter weakness, paraesthesia with self-trauma to hindlimbs, perineum or tail etc.
- the most common clinical sign is **pain on palpation of the lumbosacral area**

DEGENERATIVE PERIPHERAL NEUROPATHIES

- some peripheral neuropathies are characterised histologically chiefly by Wallerian degeneration and abortive axonal regeneration and remyelination but there is no known antecedent traumatic event
- these are therefore classified as **degenerative peripheral neuropathies**
- however, the possibility of a prior traumatic event initiating the degeneration cannot always be ruled out
- a good example is equine laryngeal hemiplegia (see below)
- some degenerative peripheral neuropathies may be congenital and due to inheritance of defective genes or exposure to teratogenic agents *in utero* or in the early post-natal period (see below)
- some degenerative peripheral neuropathies develop later in life due to exposure to neurotoxins or in association with endocrinopathies or malignant neoplasia (see below)

Equine Laryngeal Hemiplegia

- laryngeal hemiplegia is **common in horses**
- possible genetic predisposition in horses and early (or even pre-natal) onset is documented in some draught foals
- Wallerian degeneration of large myelinated axons of distal parts of the **left recurrent laryngeal nerve** → unilateral paralysis and denervation atrophy of intrinsic laryngeal muscles (especially the left dorsal cricoarytenoid muscle) → inability to abduct the left arytenoid cartilage and vocal fold → partial airway obstruction → inspiratory stridor ("roaring") and decreased athletic performance
- especially young, tall, long-necked Thoroughbreds and draught breeds (e.g. Clydesdales), with males more often affected than females

- in most cases, the cause of the Wallerian degeneration is not identifiable but previous **nerve trauma** is one possibility
- e.g. stretching or compression of the left recurrent laryngeal nerve during embryogenesis as it turns around the sixth aortic arch is one hypothesised cause
- e.g. direct nerve trauma (right or left side) during jugular venipuncture
- e.g. compression of the nerve (right or left side) by a mediastinal lymphoma

- in other horses, the clinical condition may represent a **toxic mono- or polyneuropathy** and may be uni- or bilateral (see below for toxic peripheral neuropathies)
- e.g. lead poisoning
- e.g. chronic (delayed) organophosphate poisoning
- e.g. stringhalt

CONGENITAL AND INHERITED PERIPHERAL NEUROPATHIES

Congenital Agenesis or Hypoplasia of PNS Components

- most cases of congenital agenesis or hypoplasia of PNS components are associated with severe anomalies of the CNS and of the musculoskeletal system
- some cases may be due to exposure of the fetus *in utero* to teratogenic viruses, drugs, toxins or nutritional deficiencies or excesses
- others may be inherited

Arthrogryposis

- arthrogryposis is a congenital condition in which **one or more joints is/are crookedly aligned**
- approximately 90% of cases of arthrogryposis result from **defective innervation of muscles → inadequate fetal muscle development** in the **second and third trimesters of pregnancy** → limb immobility → pre-natal joint fixation in over-flexion or over-extension by short muscles, tendons and ligaments +/- tight joint capsules
- the underlying neural abnormality may be severe (e.g. spina bifida due to arrest or delay in neural tube closure during embryogenesis) or very subtle and microscopic (e.g. segmental reduction in numbers of spinal motor neurons, failure of axons to connect with developing muscles or failure of end-plate development following contact)

Optic Nerve Hypoplasia

- optic nerve hypoplasia may accompany microphthalmia (abnormally small eyes) due to inadequate development of the optic cup from the embryonic forebrain (prosencephalon)
- e.g. in kittens exposed *in utero* to griseofulvin during optic cup development
- e.g. in piglets with hypovitaminosis A *in utero*

Congenital Colonic Agangliosis

- colonic agangliosis (**lethal white foal syndrome**) is inherited as an autosomal recessive trait in white foals born to parents with multiple spots ("frame overo" coat colour)
- analogous to Hirschsprung's disease in humans
- ganglia are absent in the myenteric plexus of the distal ileum, caecum and colon → absence of peristalsis → segmental intestinal stenosis with proximal accumulation of meconium and gas → colic and death usually within 48 hours of birth
- melanocytes are largely absent from the skin of affected foals because melanoblasts and myenteric plexus ganglionic neurons are both derived embryologically from neural crest cells

- a similar but less severe syndrome due to hypogangliosis of the myenteric plexus of the dorsal large colon, transverse colon and/or small colon is reported in Clydesdale foals in Australia and USA → megacolon by 4-9 months of age

Inherited or Familial Degenerative Peripheral Neuropathies

- many inherited or familial degenerative disorders of the PNS have been described in domestic animals, especially in particular breeds of dogs

- e.g. inherited bilateral laryngeal hemiplegia in Bouvier des Flandres, Siberian huskies, husky crosses and Dalmatians
- e.g. sensory neuropathies in English pointers, long-haired dachshunds and boxers
- e.g. "dancing doberman disease" involving the distal segments of long peripheral axons in the hindlimbs of doberman pinschers

Hypomyelinogenesis and Primary Demyelination Syndromes

- rarely, clinical PNS disease may be due to **hypomyelinogenesis** (i.e. inadequate formation of myelin by Schwann cells) or **primary demyelination** (i.e. loss of pre-formed myelin due to abnormal Schwann

cell function or formation of biochemically abnormal and unstable myelin)
- e.g. peripheral hypomyelination in golden retriever puppies
- e.g. hypertrophic polyneuropathy of Tibetan mastiffs due to failure of Schwann cells to form and maintain myelin post-natally

Myasthenia Gravis

- myasthenia gravis is a neuromuscular disease characterised by **muscle weakness** that is **exacerbated by exercise** and **alleviated by rest**
- in **generalised myasthenia gravis**, exercise → a choppy stride followed by recumbency and refusal to move; after a few minutes, the affected animal usually gets up and walks again
- **localised myasthenia gravis** may manifest as a hoarse bark or miaow, facial muscle weakness, pupillary dilation, or megaoesophagus
- myasthenia gravis can be congenital or acquired

Congenital Myasthenia Gravis

- an autosomal recessive disorder inherited in Jack Russell terriers, springer spaniels, smooth fox terriers; also reported in a few Siamese and Domestic Shorthair cats
- caused by a reduced density of acetylcholine receptors in post-synaptic muscle membranes
- clinical signs appear at 5-8 weeks of age

Acquired Myasthenia Gravis

- acquired myasthenia gravis is an **immune-mediated disorder** in which **antibodies are directed against acetylcholine receptors of neuromuscular junctions** → endocytosis and decreased density of receptors
- reported in dogs and infrequently in cats, with a possible higher incidence in German shepherd dogs and Abyssinian and Somali cats
- dogs are most commonly affected at 2-3 years or at 9-10 years of age
- a disproportionate number of affected older dogs and cats have an underlying **thymoma** and the myasthenia gravis is regarded as a **paraneoplastic syndrome**
- a few cases have been associated with hypothyroidism in dogs or with malignant neoplasms other than thymoma
- **bacterial infection** is implicated as a trigger of myasthenia gravis in humans - subunits of the acetylcholine receptor share antigenic determinants with *E. coli*, *Proteus vulgaris* and *Klebsiella pneumoniae*; a similar association has yet to be demonstrated in animals

METABOLIC PERIPHERAL NEUROPATHIES

Peripheral Neuropathies Associated with Endocrinopathies

- **endocrinopathies** such as **hypothyroidism**, **hyperadrenocorticism** and **diabetes mellitus** can occasionally manifest as peripheral polyneuropathies
- e.g. **diabetic cats** - hindlimb weakness with a plantigrade stance, depressed patellar reflexes, muscle wasting and proprioceptive deficits
- e.g. **hypothyroid dogs** - laryngeal paralysis, multiple cranial nerve deficits, hindlimb paresis, muscle wasting etc.

- distal segments of axons are commonly affected and may show histological evidence of degeneration, demyelination and remyelination
- the pathogenesis is not well understood

Peripheral Neuropathies Associated with Neoplasia

- **paraneoplastic peripheral neuropathies** are occasionally seen in dogs with **malignant neoplasia** (e.g. lymphoma or disseminated carcinomas)
- characterised by peripheral nerve demyelination, remyelination ± axonal degeneration
- clinical or subclinical paraneoplastic polyneuropathy is occasionally seen in **dogs with insulinomas** (functional malignant tumours of insulin-secreting β cells of the pancreatic islets)
- possible mechanisms include metabolic defects induced by hyperinsulinism (e.g. hypoglycaemia) or an immune-mediated process resulting from antigenic cross-reactivity between components of neoplastic islet cells and peripheral nerves

INFECTIOUS AND INFLAMMATORY PERIPHERAL NEUROPATHIES

- inflammation and necrosis of peripheral nerves and/or their secondary compression by reparative fibrosis may occur by **direct extension of inflammation or infection in adjacent structures**

- a good example is the secondary involvement of adjacent cranial nerves in horses with **mycosis** or **empyema of a guttural pouch**
- possible PNS consequences include damage to the glossopharyngeal nerve and the pharyngeal branch of the vagus nerve → ipsilateral hypoaesthesia of the pharyngeal mucosa, pharyngeal paresis, dysphagia and regurgitation
- damage to the vagus nerve → left laryngeal hemiplegia
- ± facial or vestibular nerve injury
- damage to the cervical sympathetic trunk (which carries post-ganglionic sympathetic axons to the brain) → **Horner's syndrome** (pupillary constriction, droopy eyelid, sunken eye, third eyelid prolapse and decreased sweating and increased heat on the affected side)

- inflammation of the PNS may accompany **neurotropic viral infections** (e.g. herpesviruses, rabies)

- both ***Toxoplasma gondii*** and ***Neospora caninum*** commonly cause **polyradiculoneuritis** (inflammation of multiple peripheral nerves and dorsal and/or ventral spinal nerve roots) and, to a lesser extent, **spinal ganglioneuritis** (inflammation of dorsal spinal ganglia) in dogs

- inflammatory polyneuropathies can also be a manifestation of **autoimmune disorders** such as **systemic lupus erythematosus**

Idiopathic Polyradiculoneuritis (Coonhound Paralysis)

- an **acute fulminating condition** of **dogs** and rarely **cats**
- originally described in dogs bitten or scratched by racoons, with clinical signs of ascending paralysis developing within 7-10 days of exposure → death from respiratory paralysis or slow recovery if intensively nursed
- transmissible using pooled saliva of racoons but the responsible agent was not identified
- comparable syndromes also occur in cats and dogs without exposure to raccoons

- currently considered to be a form of **autoimmune demyelination** akin to Guillain-Barré syndrome in humans (which typically follows a viral illness, vaccination or some other trigger of an aberrant immune response)
- recent research implicates infection with *Campylobacter* spp. as a major predisposing factor in both humans and dogs (e.g. following consumption of raw or undercooked chicken meat)
- the lesions comprise infiltrates of lymphocytes, plasma cells and macrophages and axonal degeneration, segmental demyelination, and attempted remyelination
- the lesions are most severe in the **ventral spinal nerve roots** and diminish distally along the peripheral nerves; there is usually only minor involvement of dorsal spinal nerve roots and ganglia
- the associated denervation atrophy of skeletal muscles can be severe

TOXIC PERIPHERAL NEUROPATHIES

- some neurotoxins may affect both the CNS and PNS (e.g. lead, chronic organophosphate poisoning)
- others may only affect the PNS
- the primary toxic injury may be to the nerve cell body, the axon, its myelin sheath or the neuromuscular junction

- **toxins that damage nerve cell bodies**
  - e.g. **organomercurial compounds** - chiefly sensory neurons
  - e.g. **doxorubicin** (a chemotherapeutic drug) - sensory and autonomic neurons

- **toxins that target peripheral axons** - often cause damage to distal parts of the long sensory or motor nerves → a “distal axonopathy” or “dying back neuropathy”, possibly by disturbing anterograde or retrograde axoplasmic flow or by inducing failure of the nerve cell body to maintain the metabolic demands of long axons
  - e.g. the chemotherapeutic agents, **vincristine**, **taxanes** and **colchicine**
  - e.g. **chronic (delayed) organophosphate poisoning** (which manifests weeks after excretion of most of the toxin)

- **toxins that cause peripheral nerve demyelination** - e.g. **lead**
  - e.g. a toxin within the plant, *Karwinskia humboldtiana* (**coyotillo** or **buckthorn**), which affects ruminants in southwest USA and Mexico

- **toxins that target neuromuscular junctions** by interfering with release of acetylcholine → lower motor neuron paralysis
  - e.g. **botulinum toxin**
  - e.g. **paralysis tick** *(Ixodes holocyclus)* **toxins**

Equine Stringhalt

- equine stringhalt is a clinical syndrome characterised by **exaggerated hindlimb flexion** and **delayed extension**
- in severe cases, there may be a bilateral bunny-hopping hindlimb gait or even forelimb involvement with carpal knuckling ± laryngeal hemiplegia

- **ordinary stringhalt** - a sporadic form that occurs world-wide
  - usually affects individual animals and is usually unilateral
  - affected animals do not usually recover

- **Australian** (or **dandelion**) **stringhalt**) - occurs in outbreak form in Australia, New Zealand and western USA
  - typically appears in late summer or autumn in arid conditions in multiple horses that have ingested Australian dandelion or flatweed (*Hypochaeris radicata*), European dandelion (*Taraxacum officinale*) or mallow (*Malva parviflora*), suggesting a toxic pathogenesis
  - spontaneous recovery is typical but may be protracted

- studies of Australian stringhalt have revealed a **distal axonopathy** with secondary demyelination and remyelination of **peroneal** and **tibial nerves** and **denervation atrophy of distal hindlimb muscles** (especially the long and lateral digital extensors, deep digital flexors, cranial tibialis and gracilis)

Dysautonomia

- dysautonomia is an acquired degenerative disorder of the autonomic division of the PNS
- reported in **cats** (**Key-Gaskell syndrome**), **horses** (and other equidae) (**grass sickness**) and **dogs**, especially in the United Kingdom
- there is as yet inconclusive evidence implicating a ***Clostridium botulinum*** **type C neurotoxin** as the cause of dysautonomia in horses
- clinical signs in **horses** largely relate to gastrointestinal stasis → intermittent vague colic over months or peracute collapse with ileus of the distal GI tract, gastric reflux and hypovolaemic shock
- clinical signs in **small animals** are more variable, e.g. megaoesophagus, dysphagia or regurgitation, urinary incontinence, mydriasis (pupillary dilation), unresponsive pupils, bradycardia, megacolon etc.
- the characteristic degenerative lesions in neuronal cell bodies in peripheral and autonomic ganglia (+/- cranial nerve nuclei in the brainstem) are microscopic and subtle (neuronal body swelling, chromatolysis +/- neuronal necrosis)

NUTRITIONAL PERIPHERAL NEUROPATHIES

- nutritional polyneuropathies are now **uncommon in domestic animals** due to provision of appropriately formulated diets

- e.g. **vitamin A deficiency** in young growing animals (especially calves and piglets) → inadequate remodelling of the skull during growth due to decreased bone resorption by osteoclasts → narrowing of the optic and other cranial nerve foramina of the skull → compression of cranial nerves (e.g. I, II, V and VIII) → blindness etc.

- e.g. **pantothenic acid deficiency** in pigs → peripheral sensory neuropathy with axonal degeneration and demyelination and secondary loss of sensory nerve bodies in dorsal spinal ganglia and dorsal root ganglia → goose-stepping gait (hypermetria), dysmetria and proprioceptive deficits

- e.g. **riboflavin** (**vitamin B_2 deficiency**) in chicks → endoneurial oedema of peripheral nerves → demyelination and mild axonal degeneration → "curled toe" paralysis

- e.g. **deficiency of vitamin E and possibly other dietary anti-oxidants** is believed to cause **equine motor neuron disease** → progressive degeneration of lower motor neurons and Wallerian degeneration of their axons → denervation atrophy of skeletal muscles and muscle fasciculations

NEOPLASIA OF THE PERIPHERAL NERVOUS SYSTEM

Peripheral Nerve Sheath Tumours

- in the past, PNS tumours of animals were subdivided into subtypes such as schwannoma, neurofibroma and neurilemmoma
- in human pathology, **schwannoma** refers to a tumour of Schwann cells whereas a **neurofibroma** contains not only Schwann cells but also perineurial cells, fibroblasts and collagen
- although these terms are still used, the current trend in veterinary pathology is to only use the terms **benign peripheral nerve sheath tumour** and **malignant peripheral nerve sheath tumour**

- peripheral nerve sheath tumours are seen most often in **dogs** and **cattle** and, to a lesser extent, **cats** and **horses**
- they may arise anywhere along peripheral nerves or from cranial or spinal nerve roots
- lesions in dogs, cats and horses often arise from **peripheral nerves of the skin or subcutis** (especially head, limbs and tail of dogs, head and neck of cats, and periocularly in horses)
- clinical signs depend on the tumour location

- in **dogs**, the tumours most commonly arise from cranial nerve roots (V and VIII) and from spinal nerve roots (roots of the brachial plexus and thoracic and lumbar spinal nerve roots)

- in **cattle**, the tumours are typically multiple, well differentiated and histologically resemble neurofibromas in humans
- there is a possible genetic basis akin to von Recklinghausen's syndrome in humans
- can be congenital or develop in calves but most are detected as incidental lesions in mature cattle at slaughter
- the most common sites in cattle are the brachial plexus, intercostal nerves, autonomic nerves of the mediastinum, epicardial plexus and hepatic autonomic plexus

- peripheral nerve sheath tumours tend to be poorly circumscribed, non-encapsulated, infiltrative masses that are difficult to completely excise
- those arising from nerve roots tend to be well-demarcated but tumour cells tend to track distally and proximally along the surface of the root/nerve
- well-differentiated tumours typically contain numerous spindle cells forming palisades, thumbprint whorls and herringbone patterns, with intervening degenerate hypocellular areas
- some tumours may be melanin-pigmented or contain foci of metaplastic bone or cartilage

- **malignant peripheral nerve sheath tumours** - most commonly diagnosed in dogs
- characterised by histological features of anaplasia
- metastasis is, however, very rarely reported

Lymphoma

- **lymphoma** involving peripheral nerves occurs infrequently in domestic animals
- in poultry, it occurs commonly as part of **Marek's disease**, a herpesvirus-induced lymphoma that may involve the CNS, PNS (especially **sciatic nerves** and **brachial plexus**) and viscera